REMARKS

Claims 1-30 and 34-64 are currently pending, with claims 1-30 and 52-56 under consideration (claims 34-51 and 57-64 having been withdrawn by the Examiner as drawn to non-elected subject matter). Claims 1, 10, 18, and 52 are amended by the present communication. None of the subject amendments adds new matter as all are supported by the specification at, for example, paragraphs [0008], [0022], and [0086], and the claims as originally filed. Applicants submit that the present amendments to the claims place the claims in condition for allowance or, at a minimum, in better condition for appeal. Accordingly, entry of the present amendment is respectfully requested. Upon entry of the present amendment, claims 1-30 and 52-56 and will remain pending and under consideration.

Rejection Under 35 U.S.C. §102 or, in the alternative, Under 35 U.S.C. §103

Claims 1-9 remain rejected, and claims 18 and 25 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Bongso *et al.* (*Human Reproduction* 9:2110-7, 1994; hereinafter "Bongso") or, in the alternative obvious over of Bongso. Applicants respectfully traverse the rejection as it applies to the pending claims for at least the reasons already of record and those that follow.

The present invention is based on the discovery that adult human cells can be used as feeder cells for growing continuous cultures of undifferentiated pluripotent human embryonic stem (hES) cells. In particular, the specification provides that "the hES cells passaged in culture using the disclosed compositions and methods have maintained a diploid karyotype and have remained in an undifferentiated state after continuous culture and many passages" (specification at paragraph [0008]). Accordingly, claim 1, as presently amended, is directed to isolated undifferentiated pluripotential hES cells, which are passage 4 or higher, have a diploid karyotype, and exhibit a dependence on adult human feeder cells or a cell-maintaining product thereof for maintenance in culture in an undifferentiated state for 4 or more passages.

The Examiner alleges that Bongso teaches isolated hES cells and asserts that all hES cells require, as an inherent property, either a feeder cell layer or feeder cell conditioned media. However, contrary to the Examiner's assertion, Bongso does not teach all of the elements of the claims as presently amended. Specifically, Bongso fails to teach undifferentiated hES cells that 1) are passage 4 or higher, and 2) have a diploid karyotype.

Bongso provides a method for isolation and culture of inner cell mass cells from human blastocysts. In particular, Bongso provides "the use of a human oviductal feeder layer together with human leukaemia inhibitory factor (HLIF) to isolate and grow ES-like cells from human embryos in culture for at least for two passages" (Bongso at p. 2110 to p. 2111, bridging sentence). Bongso provides no teaching with regard to the culturing of undifferentiated, diploid hES cells through multiple passages. Indeed, the hES cells described in Bongso did not remain in the undifferentiated state through multiple passages as required by the present claims. Specifically, Bongso reports that "[a]fter the second subculture, the cells differentiated into fibroblasts or died" (Bongso at p. 2114, col. 2, lines 7-9). Thus, Bongso does not teach or suggest undifferentiated hES cells that are passage 4 or higher and have a diploid karyotype.

Based on the reasons set forth above it is respectfully submitted that Bongso does not anticipate or render obvious the present claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 52, 54 and 55 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Xu *et al.* (*Nat Biotech* 19:971-4, 2001; hereinafter "Xu"). Applicants respectfully traverse the rejection as it applies to the pending claims.

Claim 52, as presently amended, is directed to a method for obtaining undifferentiated pluripotent hES cells by culturing a suspension of cells comprising undifferentiated pluripotent hES cells, and supportive adult human feeder cells or an hES cell-maintaining product of the feeder cells under conditions suitable for growth of the hES cells, wherein the adult human feeder cells comprise human fibroblasts from breast skin, and isolating cells that express stage-

specific surface antigen-4 (SSEA-4), Oct-4 and alkaline phosphatase, and do not express SSEA-1.

In contrast, Xu provides methods for feeder-free growth of undifferentiated hES cells. In particular, Xu evaluated growth of hES cells on Matrigel or laminin in the presence of conditioned medium from several types of cells including mouse embryonic fibroblasts (MEF), STO cells (an immortal mouse embryonic fibroblast cell line), NHG190 (a mouse embryonic cell line transfected with hTERT); BJ5ta (a human foreskin fibroblast cell line immortalized with telomerase), and hTERT-RPE (a human retinal pigment epithelial cell line immortalized with telomerase). However, Xu provides no teaching with regard to the use of human fibroblasts from breast skin as feeder cells or an hES cell-maintaining product of such feeder cells for culture of hES cells, as required by the present claims. Thus, Xu does not anticipate the present claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 10-16 and 52-56 stand rejected under 35 U.S.C. §102(e), as allegedly being anticipated by Mitalipova *et al.* (US Patent Appln. Pub. No. 2005/0037488; hereinafter "Mitalipova"). Applicants respectfully traverse the rejection as it applies to the pending claims.

Claim 10 as amended herein is directed to a culture of undifferentiated pluripotential human embryonic stem (hES) cells, comprising hES cells, wherein the hES cells are passage 4 or higher and have a diploid karyotype, and supportive adult human feeder cells, or an hES cell-maintaining product of the adult human feeder cells, wherein the adult human feeder cells comprise human fibroblasts from breast skin. Similarly, claim 52 as amended herein is directed to a method for obtaining undifferentiated pluripotent hES cells by culturing a suspension of cells comprising undifferentiated pluripotent hES cells, and supportive adult human feeder cells or an hES cell-maintaining product of the feeder cells under conditions suitable for growth of the hES cells, wherein the adult human feeder cells comprise human fibroblasts from breast skin. Applicants submit that Mitalipova does not teach all of the elements of claims 10 and 52 (and the claims depending therefrom) and thus, does not anticipate these claims.

The Examiner asserts that Mitalipova teaches the growth of hES cells on human bone marrow stromal cells, citing Mitalipova at paragraphs [0050] and [0051] and [0146]-[0156]. However, Mitalipova is silent with regard to the use of human fibroblasts from breast skin as a feeder cell layer in the culture of hES cells, as required by claim 17. Thus, Mitalipova does not anticipate claims 10-16, 52, 54, and 55. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1, 4, 15, 17, and 20 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Mitalipova *et al.* (*supra*) in view of McIntosh *et al.* (International Patent Appln. Pub. No. WO 2000/029001; hereinafter "McIntosh"). Applicants respectfully traverse the rejection as it applies to the pending claims.

The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still must be shown. Second, the combination must suggest a reasonable expectation of success. Third, the prior art reference or combination must teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references. It is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness because that the skilled artisan would not been motivated to combine the teachings of the references nor would he have had a reasonable expectation of success in achieving the present methods based on the teachings of these references.

The Examiner asserts that Mitalipova teaches a culture of hES cells grown on immortalized human skin fibroblasts and a method of obtaining an expanded population of undifferentiated pluripotent hES cells. The Examiner relies upon McIntosh for allegedly teaching the fibroblast cell line 1087sk. The Examiner further asserts that it would have been

obvious to culture the hES cells using conditioned media from CCD-1087sk cells in view of Mitalipova teaching the propagation of hES cells on skin fibroblast feeder cells. However, McIntosh, which is silent with regard to culture of undifferentiated hES cells, fails to provide any motivation to combine the teachings therein with those of Mitalipova. Thus, Applicants respectfully submit the skilled artisan would have no motivation to combine nor a reasonable expectation of success of achieving the present compositions and methods based on these references.

Moreover, Applicants submit that the art, as evidenced by Xu *et al.* (*supra*) published after the priority dates of both Mitalipova and McIntosh, teaches away from the combination of Mitalipova and McIntosh. In particular, Xu provides methods for feeder-free growth of undifferentiated hES cells. In this regard, Xu evaluated growth of hES cells on Matrigel or laminin in the presence of conditioned medium from several types of cells including mouse embryonic fibroblasts (MEF), STO cells (an immortal mouse embryonic fibroblast cell line), NHG190 (a mouse embryonic cell line transfected with hTERT); BJ5ta (a human foreskin fibroblast cell line immortalized with telomerase), and hTERT-RPE (a human retinal pigment epithelial cell line immortalized with telomerase). With respect to the use of conditioned medium from human fibroblasts in the culture of hES cells, Xu teaches that "[c]ells grown in hTERT-RPE-CM [conditioned medium] differentiated within the first week of culture" (Xu at p. 971, col. 2, lines 40-41). Xu further teaches that "[v]ery few colonies with appropriate ES morphology were found in cultures maintained in CM from STO or BJ5ta after 56 days" (Xu at p. 971, col. 2, lines 41-42). Thus, contrary to the Examiner's assertion, the data provided by Xu indicate that human fibroblasts are <u>not</u> sufficient for maintaining the pluripotency of hES cells. Thus, Xu teaches away from the present methods because the skilled artisan would be disinclined to attempt to maintain a culture of undifferentiated hES cells with conditioned media derived from the disclosed human fibroblasts or other human fibroblasts.

Thus, McIntosh's teaching of a conditioned medium from another type of human fibroblast, absent any teaching regarding its suitability of the culture of undifferentiated hES cells, does not overcome the teachings of the art (as evidenced by Xu), which teach away from the use of human fibroblasts in the culture of undifferentiated hES cells. Therefore, because

there is neither a motivation to combine the references nor a reasonable expectation of success in achieving the methods and compositions of the present claims, a *prima facie* case of obviousness has not been established. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 17, 26, 27, 29, and 30 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Mitalipova *et al.* (*supra*) in view of Lim *et al.* (U.S. Patent No. 6,921,632; hereinafter "Lim"). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Examiner asserts that Mitalipova teaches a culture of hES cells grown on immortalized human skin fibroblasts and a method of obtaining an expanded population of undifferentiated pluripotent hES cells. The Examiner further asserts that the fibroblasts are adult feeder cells producing an ES cell-maintaining product of the supportive adult human feeder cells as well as the use of the feeder cells to produce conditioned media. The Examiner cites Lim for allegedly teaching the cryopreservation of hES cells. Contrary to the Examiner's assertion, the combination of Mitalipova and Lim do not disclose all of the elements of the claims.

Claim 17 is directed to methods of obtaining an expanded population of pluripotent hES cells that require adult human feeder cells or an hES cell-maintaining product thereof, wherein the feeder cells comprise human fibroblasts from breast skin. As discussed above, Mitalipova provides no teaching with regard to the use of human fibroblasts from breast skin as feeder cells or an hES cell-maintaining product of such cells for culture of hES cells.

Moreover, Lim cannot cure the deficiencies of Mitalipova because Lim is silent with regard to the use of human fibroblasts from breast skin as feeder cells or an hES cell-maintaining product of such cells for culture of undifferentiated hES cells. Therefore, because the cited references taken alone or in combination fail to teach all of the elements of claim 17, a *prima facie* case of obviousness has not been established for independent claim 17 or for the claims depending therefrom. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

The Commissioner is hereby authorized to charge $65.00 as payment for the One-Month Extension of Time fee to Deposit Account No. 07-1896. No other fees are believed to be due with the present communication, however, the Commissioner is hereby authorized to charge any fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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